



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁴ : A61K 9/72, 9/16		A1	(11) International Publication Number: WO 87/ 05213 (43) International Publication Date: 11 September 1987 (11.09.87)
<p>(21) International Application Number: PCT/EP87/00118</p> <p>(22) International Filing Date: 27 February 1987 (27.02.87)</p> <p>(31) Priority Application Number: 19625 A/86</p> <p>(32) Priority Date: 4 March 1986 (04.03.86)</p> <p>(33) Priority Country: IT</p> <p>(71) Applicant (<i>for all designated States except US</i>): CHIESI FARMACEUTICI S.P.A. [IT/IT]; Via Palermo, 26/A, I-43100 Parma (IT).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (<i>for US only</i>) : CHIESI, Paolo [IT/IT]; PAVESI, Luciana [IT/IT]; Via Palermo, 26/A, I-43100 Parma (IT).</p> <p>(74) Agent: MINOJA, Fabrizio; Studio Consulenza Brevet- tuale, Via Rossini, 8, I-20122 Milano (IT).</p>		<p>(81) Designated States: AT (European patent), AU, BB, BE (European patent), BG, BJ (OAPI patent), BR, CF (OAPI patent), CG (OAPI patent), CH (European patent), CM (OAPI patent), DE (European patent), DK, FI, FR (European patent), GA (OAPI patent), GB (European patent), HU, IT (European patent), JP, KP, KR, LK, LU (European patent), MC, MG, ML (OAPI patent), MR (OAPI patent), MW, NL (European patent), NO, RO, SD, SE (European patent), SN (OAPI patent), SU, TD (OAPI patent), TG (OAPI patent), US.</p> <p>Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	

(54) Title: NEW PHARMACEUTICAL COMPOSITIONS FOR INHALATION

(57) Abstract

A new excipient which may be used in the preparation of pharmaceutical compositions in the form of powders for inhalation, constituted by microgranules of a conglomerate of one or more solid water-soluble diluents and a lubricant.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	ML	Mali
AU	Australia	GA	Gabon	MR	Mauritania
BB	Barbados	GB	United Kingdom	MW	Malawi
BE	Belgium	HU	Hungary	NL	Netherlands
BG	Bulgaria	IT	Italy	NC	Norway
BJ	Benin	JP	Japan	RO	Romania
BR	Brazil	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	LI	Liechtenstein	SN	Senegal
CH	Switzerland	LK	Sri Lanka	SU	Soviet Union
CM	Cameroon	LU	Luxembourg	TD	Chad
DE	Germany, Federal Republic of	MC	Monaco	TG	Togo
DK	Denmark	MG	Madagascar	US	United States of America
FI	Finland				

NEW PHARMACEUTICAL COMPOSITIONS FOR INHALATION

The present invention relates to a new excipient which may be used in pharmaceutical technology for the preparation of pharmaceutical compositions, in particular powders for inhalation.

5 The administration of drugs by aerosol is the main component of the treatment of many patients suffering from respiratory disorders with spastic complications.

10 The action of the drug is substantially accelerated and prolonged if it is inhaled; since the drug acts directly on the target organ much smaller quantities of the active principle may be used, thereby reducing side effects to a minimum.

15 The patient must synchronise his breathing correctly with the emission of the spray if pressurised aerosols or like devices are to be successfully used.

Many patients, particularly children, old people, weak patients etc. are not, however, able to use these devices correctly.

20 The ideal inhaler should enable the administration of uniform and sufficient quantities of the drug with a minimum effort on the part of the patient.

25 The direct use of powder substances in devices designed for the inhalation of these powders provides a viable alternative in the administration of bronchopulmonary drugs.

The major advantage of powder inhalers is that the active principle is released simultaneously with the act of inhalation by the patient, since the powder mist formed

- 2 -

from the particles of the active formulation is generated by the flow of air which is created by inhalation. In practice, the apparatus itself synchronises the two actions.

5 The operation of all powder inhalation devices depends on the creation of a turbulent air flow designed to disperse the particles of the drug powder in a mist suitable for inhalation.

There are two basic types of such devices which
10 differ in terms of the way in which the powder is distributed and supplied:

I. Inhalers for the administration of single doses predetermined mechanically by dividing the dosage into capsules. Such devices may be used repeatedly.
15 II. Inhalers of the dosage metering type for complete treatment cycles, which contain appropriate quantities of active principle, whose unit dose is distributed in a practical and rapid way at the time of use on the basis of the prescribed dosage, enabling, if
20 necessary, the administration of two doses simultaneously.

The supply device is finished at the end of the treatment cycle.

As a result of the relatively complicated construction of inhalers of type I, which are currently in use, patients whose ability to use their hands is impaired find them comparatively difficult to handle.
25

The fact that the dose of drug to be inhaled is contained in a gelatine capsule also entails major drawbacks:
30

- 3 -

- each time the drug is to be taken, the patient must insert a capsule in the device and, when the drug has been taken, has to empty and clean capsule and powder residues from the device;
- 5 - in many cases the capsule fails to open at the first attempt and the patient has to try a number of times;
- the capsule often fails to empty completely with the result that the patient does not take a uniform
- 10 drug dosage.

An apparatus of type II whose functional and practical features make it advantageous and convenient to use for the administration of drugs in the form of powders, is disclosed in British Patent Specification 15 2 041 763 B.

The apparatus essentially comprises the following components:

1. a mouthpiece which rotates freely on a main body;
2. a main body which, in turn, bounds:
- 20 2.1 a chamber containing the drug whose volume is such as to contain a quantity of the drug sufficient for a complete treatment cycle;
- 2.2 a metering mechanism on the base of the storage chamber which, following a rotation through 180°, supplies an exact quantity of substance equivalent to a dose of the drug;
- 25 2.3 a distributor system which causes the dose of drug supplied to fall, during rotation, into a cavity provided in the central body of the apparatus;
- 30 2.4 the above cavity, which communicates at the top

- 4 -

with the mouthpiece chamber and at the bottom with a ventilation chamber located in the space between the dose collection plate and the base baffle of the body itself. The ventilation chamber takes air 5 from two symmetrical apertures which pass through the side walls of the tank.

When the patient wishes to use the apparatus, he rotates the nozzle through 180° on the central body: this position may be visually located by lining up the two 10 arrows marked on the container and the mouthpiece at which point a catch engages.

After the dose has been metered out in this way, the patient, by breathing in from the mouthpiece, generates a flow of air into the lateral aerators.

15 The powder, taken up by the flow of air, is caused to emerge from the central cavity and inhaled directly at the time of breathing in.

If apparatus of this type is to operate correctly, the powders to be inhaled must have special properties and 20 features.

Exact metering and the accuracy of the prescribed dosage depend, for the entire duration of use of the apparatus, on the correct operation of the mechanical metering mechanism which is an essential component of the system.

25 The mechanical functions of the device and the technical properties of the content must therefore be accurately matched.

The active doses of drugs used in the treatment of respiratory infections are generally in the range of a 30 milligram or fractions thereof. For this reason, if a

uniform dosage is to be obtained, the weight of individual doses must be increased to values which enable reliable metering by diluting the active principle with a suitable inert excipient whose particle size has been monitored 5 such that it does not penetrate into the deeper sections of the respiratory tract.

The British Patent Specification 1 242 211 in the name of Fisons discloses a pharmaceutical composition in the form of a powder, formed by a mixture of micronised 10 drug substance and a pharmaceutically acceptable water-soluble excipient with a predetermined particle size distribution.

Lactose is disclosed as the preferred excipient.

Pharmaceutical compositions in powder form of this 15 type have not been found to be particularly advantageous for inhalation devices of the type disclosed in the British Patent Publication 2 041 763. Our experience shows that the powder metered out may penetrate, at the time of rotation to distribute the dose to be inhaled, into the 20 mechanism of the apparatus and, when this powder is composed of micronised active principle diluted in conventional microcrystalline excipients, tends, after a certain number of metering operations, to inhibit the free rotation of the mouthpiece on the central body by means of which the 25 drug is actually metered out. If the rotation is incomplete as a result of the resistance which is encountered, there may, towards the end of treatment, be a decrease in the unit quantity of composition supplied and therefore a decrease in the unit quantity of active principle.

50 It has now been discovered, and this is an object

- 6 -

of the present invention, that this drawback may be remedied and that the properties of pharmaceutical compositions in powder form which may be administered by inhalation using a device of the type disclosed in the British 5 Patent Publication 2 041 763 may be substantially improved if the active principle is mixed with a new type of excipient obtained by specific preparation techniques and provided with specific and special physical properties.

This new excipient, hereafter called a "conglomerate", takes the form of microgranules of a solid water-soluble vehicle such as lactose, xylitol, arabinose, dextran, mannitol or the like and a suitable lubricant such as sodium benzoate, magnesium stearate, colloidal silica, hydrogenated oils, fatty bases, etc., conglomerated in the 15 microgranule.

The conglomerate of the invention may be prepared by adding the lubricant to an aqueous solution of the vehicle. This mixture is used, by appropriate techniques, to granulate the remaining vehicle thus providing a micro-20 granulate of conglomerate from which particles less than 30 μ in diameter are finally separated by sifting the product through a 0.03 mm mesh so as to eliminate fine fractions liable to penetrate into the bronchial tree from the excipient base.

25 The vehicle may, in turn, be constituted by a mixture of powders: a mixture of lactose with 0.5 to 30% by weight of saccharose has been found to be particularly advantageous.

Granules of the type described, formed by a crushed 30 solid excipient conglomerated with a lubricant, have not

been disclosed up to now.

Their use as excipients in pharmaceutical compositions in powder form for inhalation has proved to be particularly advantageous since the flow properties of the 5 powder and its self-lubricating properties are considerably improved.

In the specific case of use of the inhaler disclosed in the British Patent Publication 2 041 763, we have found that, there is in fact a self-lubricating effect on 10 the metering mechanism.

As a result of this:

- a) the apparatus is less resistant to rotation;
- b) the weight of the composition supplied is more uniform;
- 15 c) the amount of active principle supplied during each distribution operation is more uniform.

As regards the simple physical mixture, the agglomeration of the lubricant with the excipient also has the advantage of preventing lubricant particles which are too 20 small from being inhaled and penetrating into the lungs.

Among the crushed solid excipients which are possible, latose (possibly with the addition of saccharose) and xylitol are preferred, the latter being particularly advantageous since it remedies the possible problem of 25 dental caries.

Once the conglomerate has been prepared, the pharmaceutical composition may be prepared, using appropriate techniques, by mixing the conglomerate and the active principle, in a suitable powder mixer, until they 30 are homogeneous, the active principle being in the form of

a micronised powder preferably such that at least 90% of the particles are between 0.1 and 10 μ in size.

The quantity of conglomerate with respect to the active principle will obviously vary as a function of the 5 dosage of the latter in terms of its degree of activity.

The compositions obtained in this way are metered into inhaler devices.

The formulations may contain a wide variety of drugs which may be administered by inhalation and in particular drugs used in the treatment of bronchopulmonary disorders. Specific examples of substances which may be used in the preparation of compositions of the present invention are drugs having an anti-histamine and anti-allergic action such as sodium cromoglycate and ketotifen; 15 anticholinergics such as ipratropium bromide, oxytropium bromide, thiazinamide chloride; sympathomimetic amines such as terbutaline, salbutamol, clenbuterol, pirbuterol, reproterol, procaterol and fenoterol; corticosteroids such as beclomethasone dipropionate, flunisolide, budesonide; 20 mucolytics such as ambroxol and their combinations.

The present invention also relates to a powder inhaler apparatus of the type disclosed in the British Patent Specification 2 041 763 B filled with appropriate quantities of a pharmaceutical composition of the type of 25 the present invention.

The invention is described in further detail in the following examples which do not limit it in any way.

EXAMPLE 1

Preparation of microgranules of the new vehicle (conglomerate)

1A. Composition:

Lactose F.U. (Italian Pharmacopoeia)	1000 g
Magnesium stearate	10 g
Purified water	105 g

5 A 30% (p/p) aqueous solution of lactose was prepared by dissolving 45 g of lactose F.U. in 105 g of purified water and heating it slightly. When the solution was clear, the magnesium stearate was added and mixed until it was homogeneously dispersed; the suspension was quickly 10 poured into the remaining lactose F.U. (955 g) and mixed. The mixture was passed through a 2 mm mesh and placed in an oven at 55°C. When the mixture was dry, it was granulated through a 1 mm and then a 0.212 mesh and the product was sifted through a 0.03 mm mesh eliminating the < 30 μ 15 particle fraction.

1B. Composition:

Lactose F.U.	1000 g
Sodium benzoate	20 g
Purified water	105 g

20 A 30% (p/p) aqueous solution of lactose was prepared by dissolving 45 g of lactose F.U. in 105 g of purified water and heating it slightly. When the solution was clear, the sodium benzoate was added and the mixture was stirred until the sodium benzoate was completely dissolved; the solution obtained in this way was quickly poured onto the remaining lactose F.U. (955 g) and mixed. The mixture was passed through a 2 mm mesh and placed in an oven at 55°C. When the mixture was dry, it was granulated through a 1 mm and then a 0.212 mesh. The product was then 25 sifted through a 0.03 mm mesh eliminating the < 30 μ 30 particle fraction.

- 10 -

particle fraction.

1C. Composition:

	Lactose F.U.	955 g
	Saccharose	45 g
5	Magnesium stearate	10 g
	Purified water	105 g

A 30% (p/p) aqueous solution of saccharose was prepared by dissolving 45 g of saccharose in 105 g of purified water and heating it slightly. When the solution 10 was clear, the magnesium stearate was added and mixed until it was homogeneously dispersed; the suspension was quickly poured onto the lactose F.U. (955 g) and mixed. Preparation was continued in the way described under Examples 1A and 1B.

15 1D. Composition:

Xylitol	1000 g
Sodium benzoate	10 g
Purified water	60 g

A 40% (p/p) aqueous solution of xylitol was prepared by dissolving 40 g of xylitol in 60 g of purified water and heating it slightly. When the solution was clear, the sodium benzoate was added and the mixture was stirred until the sodium benzoate was completely dissolved; the solution obtained in this way was used to granulate the remaining xylitol (960 g) in a fluidized bed. The product collected was passed through a 1 mm and then a 0.212 mm mesh. The product was then sifted through a 0.03 mm mesh eliminating the < 30 μ particle fraction.

1E. Composition:

30	Lactose F.U.	1000 g
----	--------------	--------

- 11 -

Magnesium stearate	10 g
Purified water	405 g

The lactose F.U. (1000 g) was suspended in the purified water (450 g) and the suspension heated to 70°C 5 while stirring. The magnesium stearate (10 g) was added and mixed until homogeneously dispersed. The product was atomised, under suitable conditions, to obtain the required particle size. The product was then sifted through a 0.03 mm mesh eliminating the < 30µ particle fraction.

10

EXAMPLE 2

Pharmaceutical composition in powder form for the inhalation of beclomethasone dipropionate (BDP)

A composition to be used to fill 100,000 inhaler devices of the type mentioned above, each containing 100 15 unit doses of active principle for adults and children respectively.

	Adults (kg)	Children (kg)
Micronised beclomethasone dipropionate		
	2	1
20 Lactose and magnesium stearate conglomerate	273	274

The active principle and the excipient were mixed thoroughly until homogeneous in a powder mixer. The mixture was divided and used to fill the inhaler devices by 25 means of an automatic filling device. The mouthpiece was inserted on discharge from the filling device.

EXAMPLE 3

Pharmaceutical composition in powder form for the inhalation of salbutamol

30 A composition to be used to fill 100,000 inhaler

- 12 -

devices of the type mentioned above, each containing 100 unit doses of active principle.

	kg
Micronised salbutamol	4
5 Lactose and magnesium stearate conglomerate	271

The active principle and the excipient were mixed thoroughly until homogeneous in a powder mixer. The mixture was divided and used to fill the inhaler devices by 10 means of an automatic filling device. The mouthpiece was inserted on discharge from the filling device.

EXAMPLE 4

Pharmaceutical_composition_in_powder_form_for_the_inhalation_of_a_combination_of_beclomethasone_dipropionate_(BDP)
15 and_salbutamol_at_a_ratio_of_1:2

A composition to be used to fill 100,000 inhaler devices of the type mentioned above, each containing 100 unit doses of active principle.

	kg
20 Micronised beclomethasone dipropionate	2
Micronised salbutamol	4
25 Lactose and magnesium stearate conglomerate	269

25 The active principle and the excipients were mixed thoroughly until homogeneous in a powder mixer. The mixture was divided and used to fill the inhaler devices by means of an automatic filling device. The mouthpiece was inserted on discharge from the filling device. in order to 30 check the properties of the pharmaceutical composition

- 13 -

prepared using the new conglomerate and the operation of the inhaler designed for their administration, the following tests were carried out.

TABLE 1

5 Comparison between two groups of devices for powder inhalation filled with 2 different pharmaceutical compositions formed by:

A. BDP + Lactose conglomeration with magnesium stearate
 B. BDP + Commercially available microcrystalline
 10 lactose

Parameters tested: total weight of 4 metering operations; active principle content of the quantity of composition produced by 4 metering operation; ease of rotation of the apparatus.

Compo- sition	Apparatus No.	Total weight of 4 distributions .			BDP content of 4 distributions			Ease of rotation (1)
		(in mg)			(in mcg)			
		min	max	diff(2)	min	max	diff(2)	
A BDP + lac- tose and Mg stearate agglomerate	1	109.8	117.2	7.4	765	827	62	1
	2	107.1	115.9	8.8	782	823	41	2
	3	110.8	116.4	5.6	768	828	60	2
	4	108.2	116.9	8.7	765	816	51	1
	5	108.5	117.0	8.5	786	829	43	1
	6	108.8	116.0	7.2	781	831	50	1
B BDP + commercial microcry- stalline lactose	1	93.8	102.1	8.3	712	852	140	3
	2	90.1	107.3	17.2	742	847	105	2
	3	92.6	108.1	15.5	706	848	137	1
	4	91.8	106.2	14.4	723	816	93	2
	5	90.5	103.8	13.3	715	838	123	2
	6	95.5	108.5	13.0	697	831	134	4

- 14 -

1. Arbitrary evaluation scale with values between 1 and 4 defined as follows:

1 = easy; 2 = fairly easy; 3 = difficult; 4 = very difficult.

5 2. Min = minimum value; Max = maximum value; Diff = difference BDP = beclomethasone dipropionate.

The compositions prepared using the conglomerates described in Examples 1B-1E were evaluated in a similar way and provided comparable results.

10 A further important factor of evaluation which became evident during the tests was the fact that in the case of the conglomerate the residual quantity of powder in the container chamber of the inhaler required to enable a weight distribution within acceptable limits, was sub-
15 stantially lower than that required when using the simple microcrystalline excipient (approx. 300 mg as against approx. 500 mg).

The findings illustrated clearly show that the use of the new type of excipient for pharmaceutical formulations in the form of powders to be inhaled of the invention provides substantial advantages, significantly improving reproducibility and therefore the effectiveness of a widely used form of treatment which is also used for long periods.

25 The use of pharmaceutical compositions in powder form of the type described should not be considered to be limited to the use of the specific inhaler device.

The present invention relates in fact to all industrially applicable aspects of the use of the excipient of
30 the invention, and to all combinations or formulations for which self-lubrication of the component is required (for example single pharmaceutical doses of powder, etc.).

CLAIMS.

1. An excipient suitable for use in the preparation of pharmaceutical compositions in the form of powder for 5 inhalation, constituted by microgranules of a conglomerate of one or more solid water-soluble diluents with a lubricant.
2. An excipient as claimed in claim 1, which comprises particles between 30 and 150 microns in size.
- 10 3. An excipient as claimed in claim 1 or 2, wherein the solid diluent is selected from lactose, xylitol, mannitol, arabinose and dextran or the solid diluent is lactose with the addition of saccharose at a percentage of 0.5 to 30%, preferably 4.5%.
- 15 4. An excipient as claimed in any one of the preceding claims, wherein the lubricant is selected from magnesium stearate, sodium benzoate, colloidal silica, hydrogenated oils and fatty substances.
5. An excipient as claimed in claim 1 or 2, constituted by microgranules of a conglomerate of lactose with 20 magnesium stearate.
6. An excipient as claimed in claim 1 or 2, constituted by microgranules of a conglomerate of lactose with the addition of saccharose at a percentage of 4.5% and magnesium stearate.
- 25 7. An excipient as claimed in claim 1 or 2, constituted by microgranules of a conglomerate of xylitol with sodium benzoate.
8. A pharmaceutical composition in the form of micro- 30 nized powder for inhalation, constituted by a mixture of a

- 16 -

solid drug and an excipient as claimed in any one of claims 1 to 7.

9. A pharmaceutical composition as claimed in claim 8, wherein the solid drug is crushed into particles between 5 0.1 and 10 microns in size.

10. A pharmaceutical composition as claimed in claims 8 or 9, wherein the active principle is a drug for the treatment of bronchopulmonary disorders.

11. A pharmaceutical composition as claimed in claims 8 10 to 10, wherein the active principle is an antihistamine, an antiallergic drug, a sympathomimetic amine, a steroid, an anticholinergic, a mucolytic or a mixture thereof.

12. A pharmaceutical composition as claimed in any one of claims 8 to 11, wherein the active principle is beclomethasone dipropionate, salbutamol, terbutaline, fenoterol, procaterol, pirbuterol, reproterol, clenbuterol, flunisolide, budesonide, sodium cromoglycate, ipratropium bromide, oxytropium bromide, ambroxol or a combination thereof.

20 13. A pharmaceutical composition as claimed in any one of claims 8 to 12, wherein the active principle is present at a ratio of between 0.01 and 99.5% by weight and the excipient at a ratio of between 99.9 and 0.5% by weight respectively.

25 14. A powder inhaler containing a pharmaceutical composition as defined in any one of claims 8 to 13.

15. A method for the preparation of an excipient as claimed in any one of claims 1 to 7, wherein the lubricant is added to an aqueous solution of a portion of the solid 30 diluent and the mixture obtained in this way is subsequen-

tly used for the granulation of the remainder of the solid diluent and is finally sifted through a 0.03 mm mesh to separate particles of less than 30 μ from the desired fraction.

5 16. A method as claimed in claim 15, wherein the conglomerate is obtained by granulation in a fluidised bed or by atomisation.

17. A method for the preparation of pharmaceutical compositions as claimed in any one of claims 8 to 13, 10 wherein a solid drug crushed into particles between 0.1 and 10 microns in size is mixed, in a suitable powder mixer, with an excipient of the type defined in any one of claims 1 to 7 and formed by particles between 30 and 150 microns in size.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/EP 87/00118

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC⁴: A 61 K 9/72; A 61 K 9/16

II. FIELDS SEARCHED

Minimum Documentation Searched ?

Classification System	Classification Symbols
IPC ⁴	A 61 K

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched *

III. DOCUMENTS CONSIDERED TO BE RELEVANT*

Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
Y	US, A, 3957965 (P.S. HARTLEY) 18 May 1976, see column 2, lines 15-54; column 3, lines 15-37; claims --	1-3, 8-14, 16, 17
X, Y	DE, A, 3012136 (K.K. BAUER) 1 October 1981, see claims; page 4, line 30 - page 5, line 2; page 5, paragraph 3; page 6, paragraph 3; claim 1 -----	1-17

* Special categories of cited documents: ¹⁰

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"Z" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

3rd July 1987

Date of Mailing of this International Search Report

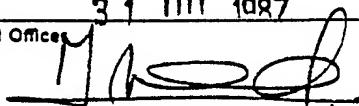
31 VIII 1987

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

M. VAN MOL



ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO.

PCT/EP 87/00118 (SA 16486)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 15/07/87

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 3957965	18/05/76	US-A- 3860618 NL-A- 6811060 FR-M- 8142 GB-A- 1242211 DE-A,C 1792207 US-A- 3634582 BE-A- 718846 CA-A- 946280 DE-A- 1792799 FR-A- 1605538 SE-B- 372420	14/01/75 11/02/69 17/08/70 11/08/71 04/11/71 11/01/72 31/01/69 30/04/74 11/08/77 23/02/79 23/12/74
DE-A- 3012136	01/10/81	None	